PTG-300 (RUSFERTIDE) TREATMENT INTERRUPTION REVERSES HEMATOLOGICAL GAINS AND RESTORES THERAPEUTIC BENEFIT ON REINITIATION IN SUBJECTS WITH POLYCYTHEMIA VERA

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INTRODUCTION

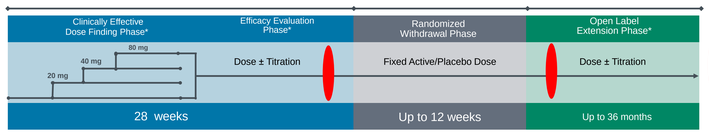
Polycythemia vera (PV) patients are treated with periodic therapeutic phlebotomy (TP) and if needed, cytoreductive therapy to maintain hematocrit (HCT) <45% to reduce the incidence of thrombosis. Constitutive erythropoiesis and repeated TP result in iron deficiency which further stimulates iron absorption and availability for robust erythropoiesis. Iron deficiency contributes to fatigue, which is the most severe and prevalent symptom for patients with PV. We have previously shown that adding rusfertide, a hepcidin mimetic, to existing PV treatment, significantly, and effectively reverses iron deficiency and essentially eliminates TP requirement for >1 year in PV patients [Hoffman ASH 2021]. Two ongoing PTG-300-04 & PTG 300-08 phase 2 studies of rusfertide in PV patients experienced an FDA-mandated brief hold which resulted in dosing interruption of rusfertide for all patients. The clinical protocols were amended to add this information, dermatological screening, and stopping rules, and rusfertide was reinitiated following patient reconsent. Majority (85%) of the patients returned for dosing.

OBJECTIVE

To examine the impact of temporary rusfertide withdrawal on iron homeostasis and TP requirements after temporary suspension in the ongoing Phase 2 rusfertide studies.

METHODS

Eligibility criteria for PTG-300-04 study (REVIVE) include PV diagnosis [by 2016 WHO criteria] and ≥3 phlebotomies with/without concurrent cytoreductive therapy in the 24 weeks before enrollment. Rusfertide 10-120 mg weekly SQ injection was added to existing cytoreductive treatment and adjusted to maintain HCT <45%. During the brief clinical hold patients were maintained on their cytoreductive regimens and had TP for HCT >45%. The clinical protocol was amended to add this information, dermatological screening, and stopping rules and rusfertide was reinitiated following patient reconsent. Most patients (85%) returned to Rusfertide add-on treatment 2-3 months after the dosing interruption and reinitiation.

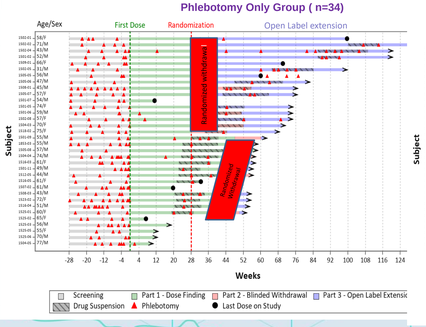


Another phase 2 Study (PTG-300-08, PACIFIC) was conducted in PV patients who had HCT >48% at baseline (on average 51%).

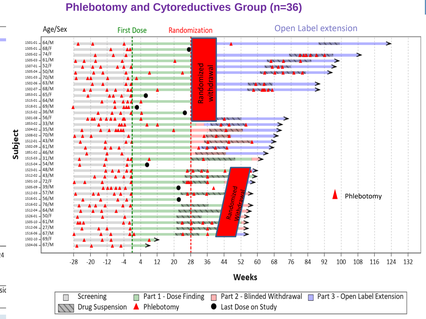
RESULTS

In REVIVE study (n=70), TP requirements in the 24 weeks before enrollment ranged from 3 to 9. Rusfertide treatment enabled consistent HCT control <45%, essentially eliminated TPs in all sub-groups, decreasing RBC count and increased MCV and MCH values. Rusfertide treatment resulted in progressive normalization of serum ferritin, suggesting a redistribution of systemic iron. During rusfertide dosing interruption, all patients had significant ($p<0.01$) increase in TPs, HCT, and RBC count; and a simultaneous decrease in MCV and serum ferritin. Patients also reported a potential of significant decrease in PV-related symptoms (i.e., increased fatigue and worsening concentration). Reinitiating rusfertide resulted in rapid normalization of hematologic parameters, elimination of TP, and improvement in symptoms demonstrating potential effectiveness of this approach.

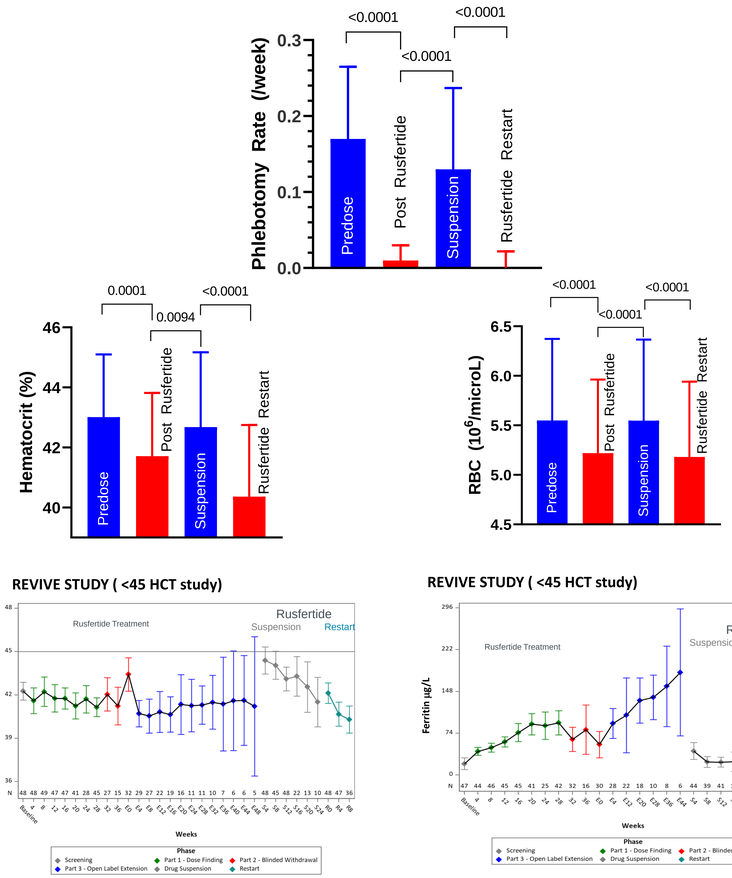
Phlebotomy Only Group (n=34)



Phlebotomy and Cytoreductives Group (n=36)



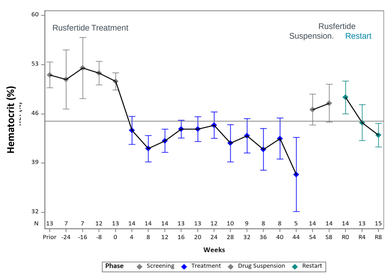
Treatment suspension rapidly reverses benefits and reinitiation restores benefits in REVIVE Study



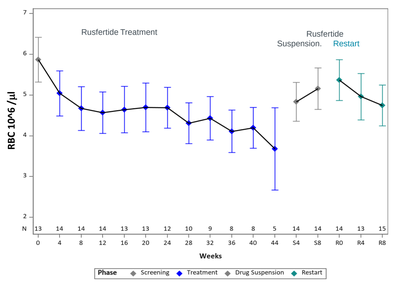
REVISE STUDY (<45 HCT study)

REVISE STUDY (<45 HCT study)

PACIFIC (High HCT study)



PACIFIC (High HCT study)



Data Cutoff May 11, 2022

Safety: Most treatment related AEs were Grade 1 or 2 ,Injection site reaction (ISRs) were most common and associated with 33% of injections. All ISRs were transient, and no patient discontinued due to an ISR. SAE's include aneurysm of popliteal artery, atrial fibrillation, chest pain, hydrocephalus, gastroenteritis, syncope, basal cell carcinoma, squamous cell carcinoma, melanoma, AML.
No grade 3 events related to rusfertide, one grade 4 event possibly related to rusfertide (asymptomatic thrombocytosis of about 1.2 million). Two withdrawals due to possibly related AE - both asymptomatic thrombocytosis (not the grade 4 subject). No clinically significant laboratory abnormalities. No Anti Drug Antibody response was noted in any patient.

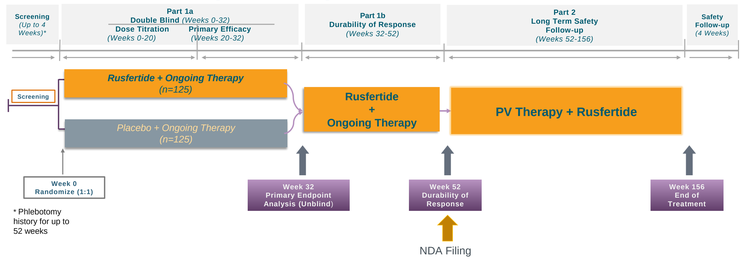
System Organ Class Preferred term	AE n (%)
Total number of Subjects	*90*
General disorders and administrative site conditions	77 (85.6)
Fatigue	19 (21.1)
Skin and subcutaneous tissue disorders	37 (41.1)
Pruritis	19 (21.1)
Hyperhidrosis	9 (10.0)
Nervous system disorders	35 (38.9)
Headache	18 (20.0)
Dizziness	14 (15.6)
Gastrointestinal disorders	32 (35.6)
Nausea	13 (14.4)
Diarrhea	11 (12.2)
Musculoskeletal and connective tissue disorders	32 (35.6)
Arthralgia	17 (18.9)
Infections and infestations	23 (25.6)
Investigations	22 (24.4)
Blood and Lymphatic Disorders	20 (22.2)
Anemia	11 (12.2)
Metabolism and nutrition disorders	17 (18.9)
Respiratory, thoracic and mediastinal disorders	16 (17.8)
Injury, poisoning and procedural complications	13 (14.4)
Psychiatric disorders	11 (12.2)
Vascular disorders	9 (10.0)

Data Cutoff May 11, 2022

CONCLUSIONS

Reversal of hematological parameters during dosing interruption and gain of hematological parameters after rusfertide restart further confirms the effect of rusfertide on both iron homeostasis and erythrocytosis. The current results support rusfertide as an effective treatment option in PV, reversing iron deficiency and essentially eliminating TP requirements in PV patients with/without cytoreductive agents. Taken together, rusfertide is a very promising novel biologic agent in both low and high-risk PV patients. A global Phase 3 trial of rusfertide in PV, VERIFY, (NCT 05210790) has been initiated.

PHASE 3 STUDY (VERIFY) SCHEMA



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